CERTIFICATE OF MAILING

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ELI LILLY AND COMPANY

By _____
Signature

12 Nov. 1982
Date

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant :	Charles D. Jones	Group Art Unit: 121
Serial No.:	331,042	Examiner: R. Schwartz
Filed :	December 16, 1981	
For :	ANTIESTROGENIC AND ANTI-ANDROGENIC BENZOTHIOPHENE	
Docket No.:	X-5526A	

DECLARATION UNDER 37 C.F.R. 1.132

James A. Clemens, Ph.D. declares as follows:

I received my Bachelor of Science degree in 1963 and my Master of Science degree in 1965 from Pennsylvania State University, majoring in biological science. I continued my studies at Michigan State University where I earned my Ph.D. in physiology in 1968. After completing my doctorate, I was awarded a one-year post-doctoral fellowship at the University of California at Los Angeles. In 1969, I entered the employ of Eli Lilly and Company where I am still employed in the central nervous system-endocrine research division. My title is Group Leader and I lead a group of twelve people. Since coming to Lilly, I have spent most of my research in the area of central nervous system research, prolactin physiology, estrogen physiology and tumors related to estrogen physiology. I am an author of about 60 papers and am named as an inventor on four U. S. patents.

I have carried out tests of a compound described in the above-named patent application, compared to an earlier related compound. The test was designed to measure their ability to reduce or inhibit the growth of tumors induced in the mammary tissue of rats by an oral dose of 7,12-dimethylbenzanthracene. The test method was described, in general, in the specification of the above-named patent application. In the test in which the

two compounds were compared, however, the daily dose of the test compounds was 0.1 mg./kg. for two weeks, 5.0 mg./kg. for two weeks, 10.0 mg./kg. for two weeks and 20 mg./kg. for two weeks. At the end of the 8 weeks, all of the rats were ovariectomized and received no treatment for two weeks. In this period of time, those tumors which were dependent on ovarian hormones could be recognized by their reduction in size. The rats were then treated for three weeks with two micrograms daily of estradiol benzoate, to re-stimulate the growth of estrogen-dependent tumors. After three weeks of estradiol treatment, the control group once more received only corn oil injections and the groups which had earlier received the test compounds once more were given daily injections of 20 mg./kg. of the same test compounds. After two weeks of these treatments, the test was terminated.

In the following table, the measurements of mammary tumors are expressed as the average total area per rat of tumors in each test group. The control column reports measurements for the untreated control animals, the compound I column reports data for 6-hydroxy-2(4-hydroxyphenyl)-3-[4-(2-piperidinoethoxy)benzoyl]-benzo[b]thiophene, and the compound II column reports data for 6-hydroxy-2-(4-hydroxyphenyl)-3-[4-(2-pyrrolidinoethoxy)benzoyl]-benzo[b]thiophene. All data is expressed as the mean plus or minus the standard error.

This Declaration does not by any means report all of the tests carried out on the piperidino compound disclosed in the above-named patent application. Tests against DMBA-induced tumors are so variable that one cannot compare the results of one test with the results of another. Thus, the only results presented are the results of the one test in which both compounds were compared side-by-side.

Table 1

	Control	Compound I	Compound II
Start	69.5 ± 15.8	58.8 ± 12.8	43.7 ± 8.6
2 weeks	267.3 ± 90.3	125.7 ± 32.8	187.6 ± 63.4
4 weeks	415.7 ± 168.6	141.2 ± 44.4	308.8 ± 89.4
5 weeks	689.9 ± 254.8	209.7 ± 74.1	588.6 ± 206.4
6 weeks	1088.5 ± 379.1	264.3 ± 115.1	758.2 ± 271.2
7 weeks	1439.1 ± 478.2	265.8 ± 114.8	854.6 ± 298.0
8 weeks	1701.5 ± 551.9	312.9 ± 161.8	845.1 ± 384.1
9 weeks	1957.1 ± 490.2	306.0 ± 150.1	963.6 ± 487.3
11 weeks	395.8 ± 129.5	194.2 ± 163.8	412.6 ± 214.2
12 weeks	327.1 ± 101.5	395.7 ± 352.2	540.8 ± 324.4
13 weeks	861.6 ± 268.7	149.6 ± 46.9	585.1 ± 235.9
14 weeks	1409.1 ± 382.2	543.4 ± 180.9	979.6 ± 490.1
15 weeks	1609.8 ± 320.9	670.9 ± 181.8	868.4 ± 315.1
16 weeks	2348.8 ± 426.2	959.8 ± 252.9	1074.9 ± 472.1

I conclude from my study of the above results that compound I, the piperidino compound, is much more effective against estrogen-dependent tumors than is compound II, which is probably not effective at all. The nature of these tests is to be highly variable, and even quite large numerical differences may not be at all significant. The differences between the two compounds in the extent to which each was able to regress the tumors, however, indicates to me that the results from compound II are not different from the results in the control animals, and that compound I was providing meaningful and useful regression of estrogen-dependent tumors.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

James A. Clemens

James A. Clemens

10/26/82

Date